REMARKS

The only claims pending are claims 15-18 and 24-28. Claims 19-23 were canceled by an Examiner's Amendment as provided in the Notices of Allowance and Allowability, mailed 19 May 2010.

Claims 15-18 and 24-28 were allowed for the reasons given on pages 2-3 of the Notice of Allowability.

In fulfillment of their Duty of Disclosure, Applicants withdrew the application from issue and submitted on 17 August 2010 a Request for Continued Examination ("RCE") under 37 C.F.R. §1.114 and an Information Disclosure Statement ("IDS") disclosing certain additional documents from the post-grant oppositions against the European member, EP-B-1 513 525 (the "European Patent"), belonging to the same patent family as the referenced U.S. patent application. The claims of the European Patent are directed to the use of a metabotropic glutamate receptor 5 ("mGluR5") antagonist for the manufacture of a medicament for the treatment of certain conditions including transient lower esophageal sphincter relaxations ("TLESRs"), gastroesophageal reflux disease ("GERD", reflux and regurgitation. The validity of the European Patent was opposed under Article 83 of the European Patent Convention ("EPC") for lack of enablement and for prior art reasons. The post-grant oppositions were disclosed by an IDS, filed 4 May 2010, i.e., prior to the mail date of the Notice of Allowance.

The same claims that were previoulsy allowed, i.e., claims 15-18 and 24-28, are now rejected under 35 U.S.C. §112, first paragraph, for lack of enablement and failure to satisfy the written description requirement. No rationale is provided in the Office Action for the Office's flip-flopping with regard to the patentability of the claimed invention. In fact, the Office Action repeats essentially the same §112 rejections which were previously withdrawn thus permitting the application to advance to allowance. For the following reasons, Applicants respectfully submit that the §112 rejections and their re-emergence following allowance without explanation are improper.

Lack of Enablement

The Examiner states that the claimed invention is not described in the specification in such a way to enable the person of ordinary skill in the art to practice the claimed invention without undue experimentation. Specifically, the Examiner alleges that the recited genus of mGluR5 antagonists is too broad in view of the disclosed species having mGluR5 antagonist activity and that there is no guidance to assist the person of ordinary skill in finding additional mGluR5 antagonists. Although the Examiner acknowledges on pages 4-5 of the Office Action that GERD is the result of incompetence of the lower esophageal sphincter and that Examples 1-3 on pages 10-13 of the specification show that disclosed species of the mGluR5 antagonist inhibit lower esophageal sphincter relaxations, the Examiner nevertheless alleges that no guidance is specifically directed to either reflux or regurgitation.

Submitted concurrently herewith is an IDS disclosing the "Decision" dated 21 October 2010 of the Opposition Division of the European Patent Office ("EPO") rejecting the post-grant oppositions lodged against the European Patent. Also disclosed is a copy of the "Minutes" of the opposition proceedings. A copy of the European Patent is also being submitted together with the IDS. For the reasons set forth in the Decision and in the Minutes, the European Patent was maintained and the oppositions were rejected.

As previously mentioned, one of the grounds for seeking revocation of the European Patent was the alleged lack of enablement pursuant to Article 83 EPC which reads as follows:

Article 83
Disclosure of the Invention

> The European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

Thus, Article 83 EPC appears to be closely related to the enablement requirement of 35 U.S.C. §112, first paragraph, which reads as follows:

35 U.S.C. §112, first paragraph
Patent Enablement

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The Examiner's attention is directed to Section 4 of the Decision at pages 6-9 and Section 2 of the Minutes at pages 1-4 for the Opposition Division's discussion regarding enablement, i.e., sufficiency of the disclosure of the invention. The Examiner will notice that many of the opponents' allegations regarding lack of enablement are similar to the Examiner's allegation as set forth in the Office Action: disclosure of only three specific compounds; no disclosure of any structure-activity relationship; and undue burden on the skilled person to define compounds having the required mGluR5 activity.

As presented during the Opposition Proceedings, the specification cites three prior art documents showing compounds having mGluR5 antagonistic activity, in addition to the three disclosed species of mGluR5 compounds, as well as screening methods to identify them as such: K. Sonogashira et al., Tetrahedron Lett. (1975), 50, 4467-4470 (See p.5, lines 20-24); WO 02/068417 (See p.12, line 3); and WO 01/12627 (Seep. 13, line 3). Applicants are providing a copy of each of the publication by K. Sonogashira et al. and WO 02/068417 concurrently with the IDS. The third document WO 01/12627 was previously disclosed by an IDS dated 28 June 2007. As evidenced by these documents which are cited in the specification, the mGluR5 receptor compounds were commonly known and several assay methods were available at the time the claimed invention was made for determining antagonistic activity of any candidate compound with respect to mGluR5.

Specifically, the Examiner's attention is directed to WO 02/68417 for the following disclosures in support of enablement:

p. 12, line 9 to page 25, line 21	mGluR5 antagonists and various generic and specific structural scopes thereof
p. 29, line 23 to page 44	several hundred examples of mGluR5 antagonists which are provided by way of illustration and not intended to be limiting in scope
p. 45, line to p. 255, line 6	detailed preparation of several specific example of mGluR5 antagonists
p. 25, line 23 to p. 26, line 26	assays for determining antagonistic activity of any test compound with respect to mGluR5
p. 255, line 8 to p. 256, line 14	assays for determining antagonistic activity of any test compound with respect to mGluR5

And with respect to WO 01/12627, the Examiner's attention is directed to the following disclosures in support of enablement:

p. 10, line 24 to page 13, line 21	mGluR5 antagonists and various generic and specific structural scopes thereof
p. 13, line 21 to page 15, line 5	more than 50 examples of mGluR5 antagonists which are provided by way of illustration and not intended to be limiting in scope
p. 19, line to p. 255, line 6	detailed preparation of more than 50 examples of mGluR5 antagonists
p. 16, line 3 to p. 17, line 6	assays for determining antagonistic activity of any test compound with respect to mGluR5
p. 46, line 10 to page 47, line 8	assays for determining antagonistic activity of any test compound with respect to mGluR5

Furthermore, the publication by K. Sonogashira et al. discloses a well-known procedure by which various MPEP-like compounds may be synthesized as well as generic scopes thereof. Thus, a scope of various MPEP-like compounds are disclosed by this publication which is cited in the specification.

In view of the foregoing support, it is evident that the specification as originally filed provides sufficient support for the genus of mGluR5 compounds as claimed and assays for detecting such compounds. With the guidance provided by the specification and the state of the art, the person of ordinary skill is fully enabled to find mGluR5 compounds within the scope of

the claims without undue experimentation. Such was the decision of the Opposition Division with respect to the European Patent and similarly claimed subject matter.

Furthermore, the preamble of all of the claims expressly recite that the patient to whom the mGluR5 antagonist is administered is a patient suffering from GERD. In other words, the claimed invention is directed to the treatment of a GERD patient who is experiencing transient lower esophageal sphincter relaxations (claim 15), GERD (claim 16) or reflux and regurgitation of gastric juice (claims 17-18).

On page 4 of the *final* Office Action, mailed 27 December 2007, the Examiner acknowledged that it is well established that TLESRs is a dominant characteristic of GERD. As disclosed in the specification at page 1, lines 26-28, the lower esophageal sphincter is prone to relaxing intermittently. As a result, fluid from the stomach can pass into the esophagus since the mechanical barrier is temporarily lacking or deficient. Such events are understood throughout the specification as "reflux". The publication Holloway & Dent, Gastroenterol. Clin. N. Amer. 19, pp 517-535 (1990) (hereinafter "Holloway & Dent") is cited on page 2, lines 1-3 of the specification, in support of the knowledge at the time the claimed invention was made that "most reflux episodes occur during...TLESRs..."

Therefore, by the express language of the claims, the condition to be treated is attributable to the recognized relationship between TLESRs, reflux and regurgitation suffered by GERD patients and not variations in intrinsic sphincter pressure, the presence or absence of an inflammatory process, etc. as proffered by the Examiner on page 5 of the Office Action. The link between TLESRs and GERD patients suffering from reflux and/or regurgitation was established in the literature and known by persons of ordinary skill in the art at the time the claimed invention was made.

The Examples show that the claimed compounds are effective in inhibiting TLESRs and thus in treating GERD and reflux and regurgitation of gastric juice in GERD patients. Enablement pursuant to 35 U.S.C. §112, first paragraph, is not an absolute standard. Experimentation by the skilled person is not fatal to enablement.

The Opposition Division of the EPO concluded that the specification was enabling in satisfaction of Art. 83 EPC. Specifically, the Opposition Division was of the opinion that the European Patent contains sufficient guidance to perform the invention in particular as:

- the receptor and compounds acting as antagonists on the receptor were known at the priority date of the patent-in-suit, and
- three examples are provided in the patent which, apart from the general disclosure, provide sufficient technical information to enable a skilled person to put the invention as claimed into practice, over the whole area claimed, with out undue burden and without needing inventive skills – the examples in the patent show how to asses if a compound is useful for the treatment of the claimed diseases.

Applicants rely on the technical reasons of the Opposition Division of the EPO for deciding in favor of enablement and sufficiency of the disclosure to practice the invention as claimed. Withdrawal of the lack of enablement rejection is requested. If the Examiner maintains the lack of enablement rejection, Applicants respectfully request the Examiner to provide a reasoning for disagreeing with the findings and Decision of the EPO, a competent examining authority.

Written Description

On pages 7-8 of the Office Action, the Examiner states that while the Examples demonstrate a percent inhibition of TLESRs in an animal model, there is inadequate written disclosure directed to various pathologies that are characterized by reflux, regurgitation and TLESRs.

As discussed in the preceding section regarding enablement, all of the pending claims are directed to the treatment of a GERD patient suffering from known symptoms of GERD: TLESRs and reflux and/or regurgitation of gastric juice. On page 4 of the *final* Office Action, mailed 27 December 2007, the Examiner acknowledged that it is well established that TLESRs is a dominant characteristic of GERD. The claims call for the administration of a therapeutically effective amount of a mGluR5 antagonist and it is submitted that the person of ordinary skill in the art, e.g., a Ph.D or M.D., with experience in the area of gastroenterology, would know the appropriate dosage regimen for treating a particular GERD patient suffering from TLESRs, reflux and/or regurgitation.

It is worth noting that the inadequate written description rejection had been withdrawn following review by a panel of Examiner's in response to Applicants' request for pre-appeal brief review. The Examiner's attention is directed to the Panel's decision, mailed 15 January 2009.

Furthermore, on page 9 of the Decision, the Opposition Division states that "antagonism on mGluR5 is useful for the treatment of the claimed diseases as an actual contribution to the art".

Applicants rely on the 15 January 2009 Panel decision and the findings of the Opposition Division and submit that the written description requirement has been met. Withdrawal of the rejection is requested.

CONCLUSION

Applicants have made a good faith attempt to respond to the Office Action. For all of the foregoing reasons, claims 15-18 and 24-28 are in condition for allowance, which action is earnestly solicited. Any fees due in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: 1 December 2010

Respectfully submitted,

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